(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 September 2001 (07.09.2001)

PCT

(10) International Publication Number
WO 01/64640 A1

(51) International Patent Classification[7]: C07D 209/08, 405/06, 409/06, A61K 31/405, A61P 29/00

(21) International Application Number: PCT/GB01/00865

(22) International Filing Date: 1 March 2001 (01.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0004961.9	1 March 2000 (01.03.2000)	GB
0004964.3	1 March 2000 (01.03.2000)	GB
0004965.0	1 March 2000 (01.03.2000)	GB
0004966.8	1 March 2000 (01.03.2000)	GB
0006975.7	22 March 2000 (22.03.2000)	GB
0006979.9	22 March 2000 (22.03.2000)	GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European

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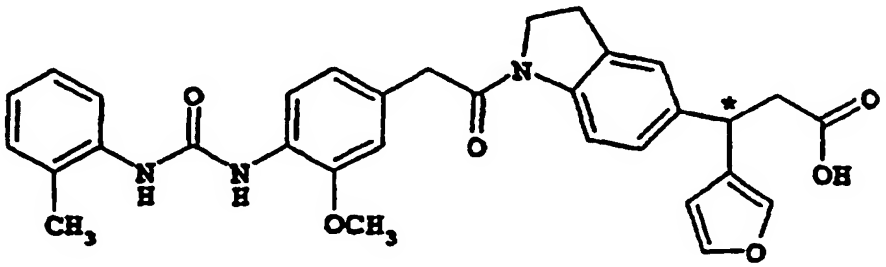
(54) Title: 2,3-DIHYDRO-1H-INDOLINYL-ALKANOIC ACIDS AS CELL ADHESION INHIBITORS



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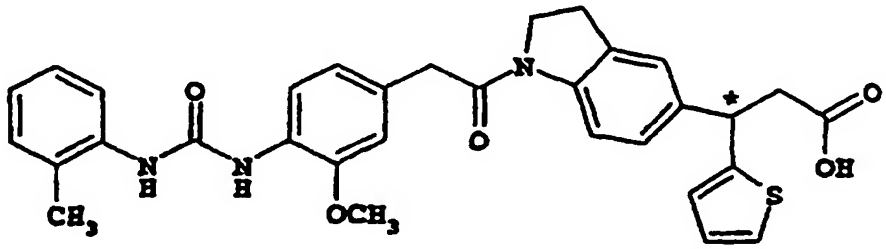

(III)

(57) Abstract: The invention is directed to selected physiologically active 2,3-dihydro-1h-indolinyl-alkanoic acids including the corresponding N-oxides and prodrugs of such compounds; and pharmaceutically acceptable salts and solvates of such compounds and their corresponding N-oxides and prodrugs. Such compounds have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4 (α4ß1). Thus, in one aspect, the present invention is directed to compounds of formula (III).

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patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations except US*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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2,3-DIHYDRO-1H-INDOLINYL-ALKANOIC ACIDS AS CELL ADHESION INHIBITORS

This invention is directed to: 3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionic acid, enantiomer A; 3-(4-fluoro-phenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A; 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid, enantiomer B; 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-5-methyl-hexanoic acid, enantiomer B; 3-furan-3-yl-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, and enantiomer A thereof; and 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionic acid, and enantiomer A thereof; and their salts and solvates, their preparation, pharmaceutical compositions containing these compound, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of cell adhesion.

Cell adhesion is a process by which cells associate with each other, migrate towards a specific target or localise within the extra-cellular matrix. Many of the cell-cell and cell-extracellular matrix interactions are mediated by protein ligands (e.g. fibronectin, VCAM-1 and vitronectin) and their integrin receptors [e.g. $\alpha 5\beta 1$ (VLA-5), $\alpha 4\beta 1$ (VLA-4) and $\alpha V\beta 3$]. Recent studies have shown these interactions to play an important part in many physiological (e.g. embryonic development and wound healing) and pathological conditions (e.g. tumour-cell invasion and metastasis, inflammation, atherosclerosis and autoimmune disease).

A wide variety of proteins serve as ligands for integrin receptors. In general, the proteins recognised by integrins fall into one of three classes: extracellular matrix proteins, plasma proteins and cell surface proteins. Extracellular matrix proteins such as collagen fibronectin, fibrinogen, laminin, thrombospondin and vitronectin bind to a number of integrins. Many of the adhesive proteins also circulate in plasma and bind to activated blood cells. Additional components in plasma that are ligands for integrins include fibrinogen and factor X. Cell bound complement C3bi and several transmembrane proteins, such as Ig-like cell adhesion molecule (ICAM-1,2,3) and vascular cell adhesion molecule (VCAM-1), which are members of the Ig superfamily, also serve as cell-surface ligands for some integrins.

Integrins are heterodimeric cell surface receptors consisting of two subunits called α and β. There are at least fifteen different α-subunits ($\alpha 1$-$\alpha 9$, α-L, α-M, α-X, α-IIb, α-V and α-E) and at least seven different β ($\beta 1$-$\beta 7$) subunits. The integrin family can be subdivided into classes based on the

β subunits, which can be associated with one or more α-subunits. The most widely distributed integrins belong to the β1 class, also known as the very late antigens (VLA). The second class of integrins are leukocyte specific receptors and consist of one of three α-subunits (α-L, α-M or α-X) complexed with the β2 protein. The cytoadhesins α-IIbβ3 and α-Vβ3, constitute the third class of integrins.

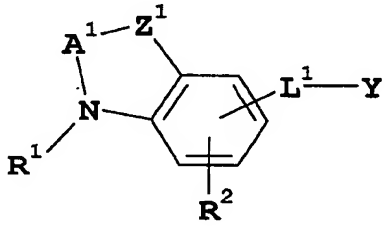
The present invention principally relates to agents which modulate the interaction of the ligand VCAM-1 with its integrin receptor α4β1 (VLA-4), which is expressed on numerous hematopoietic cells and established cell lines, including hematopoietic precursors, peripheral and cytotoxic T lymphocytes, B lymphocytes, monocytes, thymocytes and eosinophils.

The integrin α4β1 mediates both cell-cell and cell-matrix interactions. Cells expressing α4β1 bind to the carboxy-terminal cell binding domain (CS-1) of the extracellular matrix protein fibronectin, to the cytokine-inducible endothelial cell surface protein VCAM-1, and to each other to promote homotypic aggregation. The expression of VCAM-1 by endothelial cells is upregulated by proinflammatory cytokines such as INF-γ, TNF-α, IL-1β and IL-4.

Regulation of α4β1 mediated cell adhesion is important in numerous physiological processes, including T-cell proliferation, B-cell localisation to germinal centres, and adhesion of activated T-cells and eosinophils to endothelial cells. Evidence for the involvement of VLA-4/VCAM-1 interaction in various disease processes such as melanoma cell division in metastasis, T-cell infiltration of synovial membranes in rheumatoid arthritis, autoimmune diabetes, colitis and leukocyte penetration of the blood-brain barrier in experimental autoimmune encephalomyelitis, atherosclerosis, peripheral vascular disease, cardiovascular disease and multiple sclerosis, has been accumulated by investigating the role of the peptide CS-1 (the variable region of fibronectin to which α4β1 binds via the sequence Leu-Asp-Val) and antibodies specific for VLA-4 or VCAM-1 in various in vitro and in vivo experimental models of inflammation. For example, in a Streptococcal cell wall-induced experimental model of arthritis in rats, intravenous administration of CS-1 at the initiation of arthritis suppresses both acute and chronic inflammation (S.M.Wahl et al., J.Clin.Invest., 1994, 94, pages 655-662). In the oxazalone-sensitised model of inflammation (contact hypersensitivity response) in mice, intravenous administration of anti-α4 specific monoclonal antibodies significantly inhibited (50-60% reduction in the ear swelling response) the efferent response (P.L.Chisholm et al. J.Immunol., 1993, 23, pages 682-688). In a sheep model of allergic bronchoconstriction, HP1/2, an anti-α4 monoclonal antibody given intravenously or by

aerosol, blocked the late response and the development of airway hyperresponsiveness (W.M. Abraham et al. J. Clin. Invest., 1994, 93 pages 776-787).

PCT/GB99/02819 also describes VLA-4 antagonists of general formula (I):-



(I)

wherein:-

R^1 represents:

(i) R^3-Z^3-;

(ii) R^3-L^2-R^4-Z^3-;

(iii) R^3-L^3-Ar^1-L^4-Z^3-; or

(iv) R^3-L^3-Ar^1-L^2-R^4-Z^3-;

R^2 represents hydrogen, halogen, lower alkyl or lower alkoxy;

R^3 represents alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkenylalkyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycloalkyl or heterocycloalkylalkyl;

R^4 represents an alkylene chain, an alkenylene chain, or an alkynylene chain;

R^5 represents hydrogen or lower alkyl;

R^6 represents hydrogen, alkyl, alkenyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl or heteroarylalkyl;

R^7 and R^{7a} are each independently hydrogen or lower alkyl;

R^8 represents hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R^9 represents alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl, or alkyl substituted by aryl, an acidic functional group, cycloalkyl, heteroaryl, heterocycloalkyl, $-S(O)_mR^3$, $-C(=O)-NY^4Y^5$ or $-NY^4Y^5$;

R^{10} represents hydrogen, R^3 or alkyl substituted with alkoxy, cycloalkyl, hydroxy, mercapto, alkylthio or $-NY^4Y^5$;

R^{11} and R^{13} are each independently selected from hydrogen or a group consisting amino acid side chains, an acidic functional group, R^3, $-C(=O)-R^3$, or $-C(=O)-NY^4Y^5$, or alkyl substituted by an acidic functional group or by R^3, $-NY^4Y^5$, $-NH-C(=O)-R^3$, $-C(=O)-R^4-NH_2$, $-C(=O)-Ar^1-NH_2$, $-C(=O)-R^4-CO_2H$, or $-C(=O)-NY^4Y^5$;

or R^{10} and R^{11} or R^{10} and R^{12} together with the atoms to which they attached form a 3- to 6-membered heterocycloalkyl ring;

R^{12} represents C_{1-6}alkylene, optionally substituted by R^3;

R^{14} represents alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

A^1 represents a straight chain C_{1-3}alkylene linkage optionally substituted by one or more groups chosen from alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, imino, oxo, thioxo, or alkyl substituted by $-ZR^6$, $-NY^1Y^2$, $-CO_2R^6$ or $-C(=O)-NY^1Y^2$;

Ar^1 represents arylene or heteroaryldiyl;

L^1 represents:

(i) a direct bond;

(ii) an alkenylene, alkylene, alkynylene, cycloalkenylene, cycloalkylene, heteroaryldiyl, heterocycloalkylene or arylene linkage each optionally substituted by (a) an acidic functional group, cyano, oxo, $-S(O)_mR^9$, R^3, $-C(=O)-R^3$, $-C(=O)-OR^3$, $-N(R^8)-C(=O)-R^9$, $-N(R^8)-C(=O)-OR^9$, $-N(R^8)-SO_2-R^9$, $-NY^4Y^5$ or $-[C(=O)-N(R^{10})-C(R^5)(R^{11})]_p-C(=O)-NY^4Y^5$, or by (b) alkyl substituted by an acidic functional group, or by $S(O)_mR^9$, $-C(=O)-NY^4Y^5$ or $-NY^4Y^5$;

(iii) a $-[C(=O)-N(R^{10})-C(R^5)(R^{11})]_p-$ linkage;

(iv) a $-Z^2-R^{12}-$ linkage;

(v) a $-C(=O)-CH_2-C(=O)-$ linkage;

(vi) a $-R^{12}-Z^2-R^{12}-$ linkage;

(vii) a $-C(R^4)(R^{13})-[C(=O)-N(R^{10})-C(R^5)(R^{11})]_p-$ linkage; or

(viii) a $-L^5-L^6-L^7-$ linkage;

L^2 represents a $-NR^5-C(=Z)-NR^5-$, $-C(=Z)-NR^5-$, $-C(=O)-$, $-C(=Z)-O-$, $-NR^5-C(=Z)-$, $-Z-$, $-S(O)_m-$, $-NR^5-$, $-SO_2-NR^5-$, $-NR^5-SO_2-$, $-NR^5-C(=O)-O-$, $-O-C(=O)-$, or $-O-C(=O)-NR^5-$ linkage;

L^3 represents a heteroaryldiyl, $-NR^5-C(=Z)-NR^5-$, $-C(=Z)-NR^5-$, $-C(=Z)-O-$, $-NR^5-C(=Z)-$, $-Z-$, $-S(O)_m-$, $-NR^5-$, $-SO_2-NR^5-$, $-NR^5-SO_2-$, $-NR^5-C(=O)-O-$, $-O-C(=O)-$, or $-O-C(=O)-NR^5-$ linkage;

L^4 represents a direct bond, an alkylene, alkenylene or alkynylene chain;

L^5 and L^7 each independently represent a direct bond or an alkylene chain;

L^6 represents a cycloalkylene or heterocycloalkylene linkage;

Y^1 and Y^2 are independently hydrogen, alkenyl, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group $-NY^1Y^2$ may form a cyclic amine;

Y^4 and Y^5 are independently hydrogen, alkenyl, alkyl, alkynyl, aryl, cycloalkenyl, cycloalkyl, heteroaryl, heterocycloalkyl, or alkyl substituted by alkoxy, aryl, cyano, cycloalkyl, heteroaryl, heterocycloalkyl, hydroxy, oxo, $-NY^1Y^2$, or one or more $-CO_2R^8$ or $-C(=O)-NY^1Y^2$ groups; or the group $-NY^4Y^5$ may form a 5- to 7-membered cyclic amine which (i) may be optionally substituted with one or more substituents selected from alkoxy, carboxamido, carboxy, hydroxy, oxo (or a 5-, 6- or 7-membered cyclic acetal derivative thereof), R^{10}; (ii) may also contain a further heteroatom selected from O, S, SO_2, or NY^6; and (iii) may also be fused to additional aryl, heteroaryl, heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system;

Y^6 represents hydrogen, alkyl, aryl, arylalkyl, $-C(=O)-R^{14}$, $-C(=O)-OR^{14}$ or $-SO_2R^{14}$;

Z is an oxygen or sulfur atom;

Z^1 is $C(R^7)(R^{7a})$, C(=O) or CH(OH);

Z^2 is O, $S(O)_n$, NR^5, $SONR^5$, $C(=O)NR^5$ or C(=O);

Z^3 is a direct bond, C(=O), OC(=O), $NR^5C(=O)$, or SO_2;

m is an integer 1 or 2;

n is zero or an integer 1 or 2;

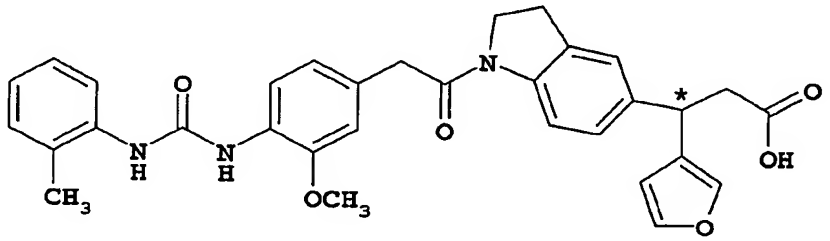
p is zero or an integer 1 to 4; and

Y is carboxy (or an acid bioisostere);

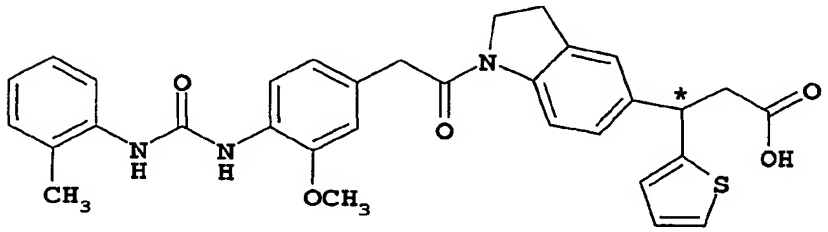
and the corresponding N-oxides, and their prodrugs; and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their N-oxides and prodrugs, but excluding compounds where an oxygen, nitrogen or sulfur atom is attached directly to a carbon carbon multiple bond of an alkenylene, alkynylene or cycloalkenylene residue.

We have now found that specific compounds generally embraced within PCT/GB99/02819 have particularly advantageous pharmaceutical properties in their ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4 ($\alpha 4\beta 1$).

Thus, in one aspect, the present invention is directed to compounds of formula (II) or (III):-



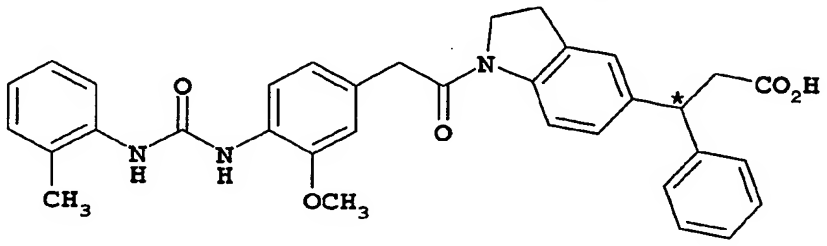
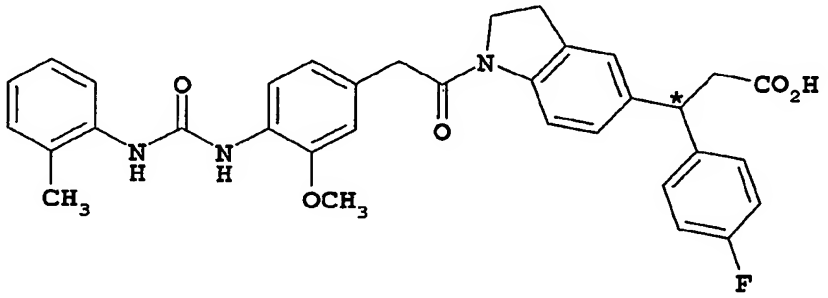
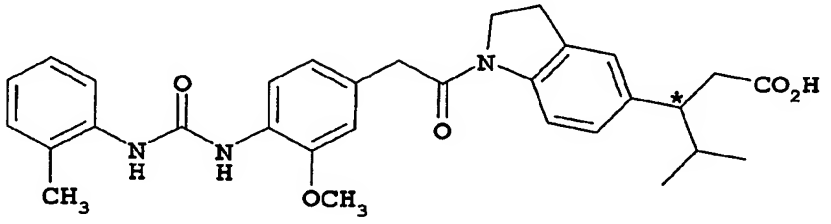
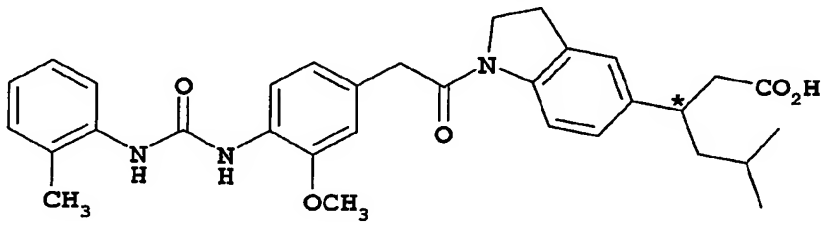
(II)



(III)

as racemic mixtures [compounds (II) and (III) have an optical centre at the * position] and as their active enantiomers (enantiomers A); and pharmaceutically acceptable base addition salts and solvates (e.g. hydrates) of such compounds.

In another aspect the present invention is directed to compounds A2-B2-C7, A2-B2-C8, A2-B2-C5 and A2-B2-C6, of formula (IV), (V), (VI) and (VII), described in PCT/GB99/02819 as VLA-4 antagonists.

A2-B2-C7	 (IV)
A2-B2-C8	 (V)
A2-B2-C5	 (VI)
A2-B2-C6	 (VII)

Compounds of formula (IV), (V), (VI) and ((VII) have an optical centre at the ⋆ position and these compounds are described in PCT/GB99/02819 as the racemic mixtures. We have now found that one of the enantiomers of each racemate (IV), (V), (VI) and ((VII) has enhanced pharmaceutical properties compared to its racemic mixture as illustrated hereinafter. Thus the

present invention is directed to 3-phenyl-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A; 3-(4-fluoro-phenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A; 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid, enantiomer B and 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-5-methyl-hexanoic acid, enantiomer B, and pharmaceutically acceptable base addition salts and solvates (e.g. hydrates) of these compounds.

Base addition salts of the compounds of the invention may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including those derived from alkali and alkaline earth metal salts, within the scope of the invention include those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

As well as being useful in themselves as active compounds, base addition salts of the compound of the invention are useful for the purposes of purification of the compound of the invention for example by exploitation of the solubility differences between the salts and the parent compound, side products and/or starting materials by techniques well known to those skilled in the art.

The compounds of the invention exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. The present invention thus provides, according to a further aspect, compounds of the invention and compositions containing compounds of the invention for use in therapy.

Compounds within the scope of the present invention block the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha4\beta1$) according to tests described in the literature and described in vitro and in vivo procedures hereinafter, and which tests results are believed to correlate to pharmacological activity in humans and other mammals. Thus, in a further embodiment, the present invention provides compounds of the invention and compositions containing compounds of the invention for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha4\beta1$ mediated cell adhesion. For example, compounds of the present invention are useful in the treatment of inflammatory diseases, for example joint inflammation, including arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis. Additionally, the compounds may be useful in the treatment of acute synovitis, autoimmune diabetes, autoimmune encephalomyelitis, colitis, atherosclerosis, peripheral vascular disease, cardiovascular disease, multiple sclerosis, asthma, psoriasis restenosis, myocarditis, inflammatory bowel disease and melanoma cell division in metastasis.

A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

Another special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

Another special embodiment of the therapeutic methods of the present invention is the treating of inflammatory bowel disease.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha4\beta1$), for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of a compound of the invention or a composition containing a compound of the invention. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha4\beta1$), and thus producing the desired therapeutic effect.

References herein to treatment should be understood to include prophylactic therapy as well as treatment of established conditions.

The present invention also includes within its scope pharmaceutical compositions comprising at least one of the compounds of the invention in association with a pharmaceutically acceptable carrier or excipient.

Compounds of the invention may be administered by any suitable means. In practice compounds of the present invention may generally be administered parenterally, topically, rectally, orally or by inhalation, especially by the oral route.

Compositions according to the invention may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavourings, colourings, or stabilisers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient

quantity of glucose or sodium chloride and that they are sterilised by heating, irradiation or microfiltration.

For topical administration, gels (water or alcohol based), creams or ointments containing compounds of the invention may be used. Compounds of the invention may also be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier.

For administration by inhalation compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebuliser or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The compounds according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. Of course, for some patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds of the invention may be prepared by the process described in Example and Reference Examples section. Alternatively, compounds of formula (II), enantiomer A; (III), enantiomer A; (IV), enantiomer A; (V), enantiomer A; (VI), enantiomer B; and (VII), enantiomer B, may be separated from the corresponding racemic mixture by the application or adaptation of known methods, for example: (i) chiral chromatographic techniques [e.g. those described in (a) Preparation of drug enantiomers by chromatographic resolution on chiral stationary phases by Francotte, Eric. Chem. Anal. (N. Y.), 1997, 142 (Impact of Stereochemistry on Drug Development and Use), pages 633-683 and (b) Chiral Separations by HPLC, 1989, edited by Krstulovic, A. M. and published by Ellis Horwood, Chichester, UK] and (ii) resolution via chiral amine salts such as α-methylbenzylamine or ephedrine salts [e.g. those described for the resolution of α-arylpropionic acids in UK Patent Application Publication No. GB 2328208].

According to a further feature of the invention, base addition salts of the compound of the invention may be prepared by reaction of the free acid with the appropriate base, by the application or adaptation of known methods. For example, the base addition salts of the compounds of this invention may be prepared either by dissolving the free acid in water or aqueous alcohol solution or other suitable solvents containing the appropriate base and isolating the salt by evaporating the solution, or by reacting the free acid and base in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The present invention is further exemplified by the following illustrative Example and Reference Examples.

High Pressure Liquid Chromatography/ Mass Spectrometry [MS(ES)] conditions were as follows: 3 micron Luna C18 (2) HPLC column (30mm x 4.6mm) operated under gradient elution conditions with mixtures of (A) water containing 0.1% formic acid and (B) acetonitrile containing 0.1% formic acid as the mobile phase [0.00 minutes, 95%A:5%B; 0.50 minutes, 95%A:5%B; 4.50 minutes, 5%A:95%B; 5.00 minutes, 5%A:95%B; 5.50 minutes, 95%A:5%B]; flow rate 2ml/minute with approximately 200μl/minute split to the Mass Spectrometer; injection volume 10-40μl; in line Diode Array (220-450nm), in line Evaporative light scattering (ELS) detection ELS - temperature 50°C, Gain 8 - 1.8ml/minute; Source temperature 150°C.

EXAMPLE 1

3-(1-{[3-Methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionic acid, enantiomer A

A suspension of ethyl 3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate, enantiomer A [0.27g, Reference Example 1(a)] in ethanol (35mL), under argon, was treated with sodium hydroxide solution (1.2mL, 1M) and then heated at reflux for 1.5 hours. The cooled reaction mixture was evaporated. The residue was treated with water (30mL) with gentle warming to complete solution and the solution was acidified to pH 1 by addition of hydrochloric acid (1M). The resulting precipitate was washed three with water (5mL) and then dried at 60°C under high vacuum to the title compound (0.24g). MS(ES): 564 (MH^+), 586 (MNa^+). HPLC on chiral stationary phase [Chiralpak AD column(25cm x 4.6mm) using a mixture of heptane, ethanol and trifluoroacetic acid (190:60:0.5, v/v/v) as mobile phase with a flow rate of 1mL/minute and UV detection at 254nm]: retention time (R_T) = 60minutes.

EXAMPLE 2

3-(4-Fluoro-phenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A

A suspension of ethyl 3-(4-fluorophenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)- propionate, enantiomer A [0.1g, Reference Example 1(b)] in ethanol (10mL) was warmed gently until solution was achieved, then, under argon, aqueous sodium hydroxide (0.4mL, 1M) was added. The mixture was stirred at room temperature for 1.5 hours, then diluted with ethanol (10mL), then heated at 50°C for 1hour and then heated at reflux for 1.5 hours. The reaction mixture was cooled to room temperature then evaporated. The residue was treated with water (10mL) and tetrahydrofuran (2mL) and the pH of this mixture was adjusted to 1 by addition of hydrochloric acid (1M). The resulting precipitate was filtered, washed three times with water (5mL) and dried at 60°C under high vacuum to afford the title compound (0.09g). MS(ES): 582 (MH^+), 604 (MNa^+). HPLC: R_T = 67 minutes.

EXAMPLE 3

3-(1-{[3-Methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid, enantiomer B

A solution of 3-(2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid ethyl ester, enantiomer B [290mg, Reference Example 6(a)] in dimethylformamide and treated successively with [3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetic acid (420mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (500mg) and diisopropylethylamine (0.5mL). After

standing at room temperature overnight the mixture was partitioned between ethyl acetate (100mL) and dilute hydrochloric acid (100mL) and the layers were separated. The organic phase was washed with sodium hydrogen carbonate solution (100mL, 5% w/v), then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (1:1, v/v) to give a colourless gum (700mg). A solution of this gum in a mixture of methanol (40mL) and tetrahydrofuran (10mL) was treated with lithium hydroxide solution (10mL, 1M) and the mixture was stirred at 40°C for 2 hours then evaporated to low bulk. The residue was diluted with water (20mL) and the mixture was acidified by addition of hydrochloric acid (1M). The resulting white precipitate was filtered, then washed with water, then with ether and then dried to give the title compound (420mg) as a white foam. HPLC: R_T = 16.7 minutes (98.6 % by ELS). MS (ES): 552(MNa^+), 528(M^-).

EXAMPLE 4

3-(1-{[3-Methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-5-methyl-hexanoic acid, enantiomer B

A solution of 3-(2,3-dihydro-1H-indol-5-yl)-5-methyl-hexanoic acid ethyl ester, enantiomer B [670mg, Reference Example 6(b)] in dimethylformamide (10mL) was treated successively with [3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetic acid (770mg), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (930mg) and diisopropylethylamine (0.85mL). After standing at room temperature for 2 hours the mixture was partitioned between ethyl acetate and water and the layers were separated. The organic layer was washed with hydrochloric acid (0.5M), then with sodium hydrogen carbonate solution (5% w/v), then with brine, then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (1:1, v/v) to give a colourless gum (1.2g). The gum was dissolved in a mixture of methanol (50mL) and tetrahydrofuran (20mL) and the solution was treated with lithium hydroxide solution (10mL, 1M). After stirring at 40°C for 1 hour, then standing at room temperature overnight this mixture was evaporated to low bulk. The residue was diluted with water (20mL) and the mixture acidified with hydrochloric acid (1M). The resulting white precipitate was extracted into ethyl acetate. The layers were separated and the organic layer was washed with brine, then dried and then evaporated. The resulting white solid was triturated with ether to give the title compound (1.0g) as a white solid. HPLC: R_T = 17.3 minutes (100 % by ELS). MS(ES): 566(MNa^+), 544 (MH^+), 542 (M^-).

EXAMPLE 5

3-Furan-3-yl-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-propionic acid, enantiomer A

A solution of ethyl 3-furan-3-yl-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-propionate, enantiomer A [0.92g, Reference Example 1(c)] in methanol (20mL) was treated with a solution of lithium hydroxide monohydrate (0.4g) in water (5mL). After stirring at room temperature for 4 hours the mixture was evaporated to low bulk and then treated with hydrochloric acid (20mL, 1M). The resulting precipitate was taken up in ethyl acetate (20mL) and the solution was triturated with ether to give an off-white crystalline solid. This was collected by filtration and dried to give the title compound (0.74 g) as a white crystalline solid. LC-MS: R_T = 3.47 minutes (100%); MS 554 (MH^+), 576 (MNa^+). HPLC on chiral stationary phase [Chiralpak AD column(25cm x 4.6mm) using a mixture of heptane, methanol, ethanol, isopropanol and trifluoroacetic acid (175:60:10:10:1, v/v/v/v/v) as the mobile phase with a flow rate of 1mL/minute and UV detection at 254nm]: R_T = 29 minutes (> 98% by peak area).

EXAMPLE 6

(RS)-3-Furan-3-yl-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-propionic acid

(RS)-5-(2-Ethoxycarbonyl-1-furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester [2.2g, Reference Example 11(a)] was dissolved in trifluoroacetic acid (5mL) and the solution kept at room temperature for 30 minutes and then evaporated. The residue was dissolved in dimethylformamide (50mL) and the solution was treated successively with [3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetic acid (2.2g), *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.35g), and diisopropylethylamine (5.2g). After standing at room temperature overnight the reaction mixture was evaporated to low bulk. The residue was partitioned between ethyl acetate (200mL), and hydrochloric acid (200mL, 1M). The organic phase was washed with sodium hydrogen carbonate solution (100mL, 5% w/v), then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane mixture (2:3, v/v) to yield a colourless gum (1.9g). The gum was dissolved in ethanol (50mL) and the solution was treated with sodium hydroxide solution (5mL, 1M). After standing at room temperature overnight the mixture was evaporated to low bulk. The residue was taken up in water and the solution was acidified with hydrochloric acid (1M). The resulting precipitate crystallised on the addition of ether (50mL). This material was collected by filtration, then washed with water, then with ether and then dried to give the title compound (1.5g) as a white powder. LC-MS: R_T = 3.47 minutes (100%); MS 554 (MH^+), 576 (MNa^+).

EXAMPLE 7

3-(1-{[3-Methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionic acid, enantiomer A

A solution of ethyl 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionate, enantiomer A [1.45g, Reference Example 1(d)] in a mixture of methanol (25mL) and tetrahydrofuran (25mL) was treated with lithium hydroxide solution (10mL, 1M). After standing at room temperature overnight the mixture was evaporated to low bulk and the residue was dissolved in water (20mL). The solution was acidified with dilute hydrochloric acid (1M) to give a white precipitate. The mixture was extracted with ethyl acetate (50mL). On standing a white precipitate was formed in the ethyl acetate extract. This was collected by filtration and dried to give the title compound (1.22g) as a white crystalline solid. LC-MS: R_T = 3.57 minutes (100 %); MS 570 (MH^+), 592 (MNa^+). HPLC on chiral stationary phase [Chiralpak AD column (25cm x 4.6 mm) using heptane/ethanol/trifluoroacetic acid 190:60:0.5, v/v/v as mobile phase running at 1mL/minute and UV detection at 254nm]: R_T = 63 minutes (98.5 % by peak area).

EXAMPLE 8

(RS)-3-(1-{[3-Methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionic acid

A solution of ethyl (RS)-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionate [200mg, Reference Example 11(b)] in a mixture of methanol (5mL) and tetrahydrofuran (5mL) was treated with sodium hydroxide solution (3mL, 1M). After standing at room temperature overnight the reaction mixture was evaporated to low bulk, then diluted with water (10mL) and then acidified with dilute hydrochloric acid. The resulting precipitate was collected by filtration, then washed with water and then dried to give the title compound (155 mg) as a white powder. LC-MS: R_T = 3.57 minutes (100 %); MS 570 (MH^+), 592 (MNa^+).

REFERENCE EXAMPLE 1

(a) Ethyl 3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate, enantiomer A

A solution of ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate, enantiomer A [0.28g, Reference Example 2(a)] in dry dichloromethane (7mL) at 0°C was treated

with trifluoroacetic acid (2.3mL). The cooling bath was removed and the mixture stirred for 1hour then evaporated. The residue was chased with toluene (10mL) and the resulting gum was partitioned between ethyl acetate (15mL) and saturated aqueous sodium bicarbonate(10mL). The organic phase was washed with brine (10mL), then dried over magnesium sulfate and then evaporated. The residual gum (0.14g) was dissolved in dry dimethylformamide (10mL). This solution was treated with O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.2g) under an argon atmosphere, and after stirring for 10 minutes the mixture was treated with diisopropylethylamine (0.25mL) and a solution of 3-methoxy-4-(3-o-tolyl-ureido)-phenylacetic acid (0.16g) in dry dimethylformamide (5mL). The reaction mixture was stirred for a further 3.5 hours, then allowed to stand for 4 days and then evaporated under high vacuum. The residue was treated with water (25mL) and hydrochloric acid (2mL, 1M) and then extracted twice with ethyl acetate (15mL). The extracts were washed twice with water (15mL), then with brine (15mL), then dried over magnesium sulfate and then evaporated. The residue was subjected to flash chromatography on silica under gradient elution conditions with mixtures of cyclohexane and ethyl acetate (2:1, v/v to 1:1, v/v) to give the title compound (0.28g) as a foam. MS(ES): R_T = 4.09 minutes; 592(MH^+), 614(MNa^+).

(b) By proceeding in a similar manner to Reference Example 1(a) but using ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-propionate, enantiomer A [Reference Example 2(b)] and subjecting the crude product to flash chromatography on silica under gradient elution conditions with mixtures of pentane and ethyl acetate (2:1 v/v to 1:1 v/v) there was prepared ethyl 3-(4-fluorophenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)- propionate, enantiomer A as a solid. MS(ES): R_T = 4.11 minutes; 619(MH^+), 632(MNa^+).

(c) By proceeding in a similar manner to Reference Example 1(a) but using 5-(2-ethoxycarbonyl-1-furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid *tert*-butyl ester, enantiomer A [Reference Example 2(c)] and subjecting the crude product to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (1:1, v/v) there was prepared ethyl 3-furan-3-yl-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-propionate, enantiomer A as an off-white solid.

(d) By proceeding in a similar manner to Reference Example 1(a) but using 5-(2-ethoxycarbonyl-1-thiophen-2-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, enantiomer A [Reference Example 2(d)] and subjecting the crude product to flash chromatography

on silica eluting with a mixture of ethyl acetate and cyclohexane (1:1, v/v) there was prepared ethyl 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionate, enantiomer A as a white foam.

REFERENCE EXAMPLE 2

(a) Ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate, enantiomer A

A mixture of ethyl (RS)-3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate [Reference Example 3(a)] was separated on a preparative CHIRALPAK AD column (25cm x 2cm) (Daicel Chemical Industries Ltd) using a mixture of heptane and isopropanol (99:1, v/v) as the mobile phase at a flow rate of 15mL/minute and a loading of 142mg Reference Example 3 in 2ml of mobile phase. Under these conditions the first eluate was the title compound.

(b) By proceeding in a similar manner to Reference Example 2(a) but separating a mixture of ethyl (RS)-3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-propionate [Reference Example 3(b)] using a mixture of heptane and ethanol (9:1, v/v) as the mobile phase at a flow rate of 8mL/minute and a loading of 165mg Reference Example 3(b) in 2ml of mobile phase there was obtained as the second eluate ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-propionate, enantiomer A.

(c) By proceeding in a similar manner to Reference Example 2(a) but separating a mixture of mixture of (RS)-5-(2-ethoxycarbonyl-1- furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid *tert*-butyl ester [Reference Example 11(a)] using a mixture of isopropyl alcohol and hexane (1:99, v/v) as the mobile phase at a flow rate of 15mL/minute there was obtained as the first eluate 5-(2-ethoxycarbonyl-1- furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid *tert*-butyl ester, enantiomer A.

(d) By proceeding in a similar manner to Reference Example 2(a) but separating a mixture of mixture of (RS)-5-(2-Ethoxycarbonyl-1-thiophen-2-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [Reference Example 11(b)] using a mixture of isopropyl alcohol and hexane (1:99, v/v) as the mobile phase at a flow rate of 15mL/minute there was obtained as the first eluate 5-(2-ethoxycarbonyl-1-thiophen-2-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, enantiomer A.

REFERENCE EXAMPLE 3

(a) Ethyl (RS)-3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate

A solution of [E/Z]-ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-prop-2-enoate [4.9g, Reference Example 4(a)] in ethanol (280mL) was hydrogenated at 50°C using 10% palladium on charcoal catalyst (0.5g) for 18 hours. The mixture was filtered through a pad of diatomaceous earth and the pad was washed twice with ethanol (50mL). The combined filtrate and washings were evaporated and final traces of ethanol were removed under high vacuum to give the title compound as a colourless oil. MS(ES): R_T = 4.41 minutes; 418(MNa^+).

(b) By proceeding in a similar manner to Reference Example 3(a) but using [E/Z]-ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-prop-2-enoate [Reference Example 4(b)] there was prepared ethyl (RS)-3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-propionate as a clear gum. MS(ES): R_T = 4.41 minutes; 436(MH^+).

REFERENCE EXAMPLE 4

(a) [E/Z]-Ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-phenyl-prop-2-enoate

A mixture of tri-*o*-tolylphosphine (1.2g), tributylamine (27mL) and palladium diacetate (0.4g) were added to a solution of 5-bromo-1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indole (8g, Reference Example 5) and ethyl cinnamate (9.45g) in dimethylformamide (65mL). The mixture was stirred and heated at 140°C under a nitrogen atmosphere for 16 hours, then cooled to room temperature and then evaporated under high vacuum. The residue was dissolved in ethyl acetate (500mL) and the solution was washed four times with hydrochloric acid (150mL, 0.5M), then with water (100mL), then twice with saturated aqueous sodium bicarbonate (150mL), then with brine (150mL), then dried over magnesium sulfate and then evaporated. The residual oil was subjected to flash chromatography on Brockman alumina under gradient elution conditions with mixtures of cyclohexane and diethyl ether (19:1, v/v to 7:3, v/v) to give the title compound (2.1g) as a viscous yellow oil. MS(ES): R_T = 4.59 minutes; 416(MNa^+).

(b) By proceeding in a similar manner to Reference Example 4(a) but using ethyl 4'-fluorocinnamate to replace ethyl cinnamate and subjecting the crude product to flash chromatography on alumina under gradient elution conditions starting with cyclohexane and finishing with a mixture of cyclohexane and diethyl ether (9:1, v/v) there was prepared [E/Z]-ethyl 3-(1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indol-5-yl)-3-(4-fluorophenyl)-prop-2-enoate as a yellow gum. MS(ES): R_T = 4.6 minutes; 434(MNa^+).

REFERENCE EXAMPLE 5

5-Bromo-1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indole

5-bromoindoline (10g) was added in one portion to molten di-tertiary-butyl dicarbonate (11.6g) at 30-40°C (immediate effervescence was followed by the formation of a solid cake). The reaction mixture was triturated with pentane and the product collected by filtration to give the title compound (15g) as a white powder.

REFERENCE EXAMPLE 6

(a) 3-(2,3-Dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid ethyl ester, enantiomer B

A stirred solution of 5-{2-methyl-1-[(1-phenyl-ethylcarbamoyl)-methyl]-propyl}-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, diastereoisomer B [.(1.8g, Reference Example 7(a)] in acetic acid (10mL) was treated with concentrated hydrochloric acid (100mL) was heated at 95°C for 48 hours then evaporated. The residue was dissolved in ethanol (100mL) containing concentrated sulfuric acid (5 drops) and the solution was stirred at reflux for 5 hours and then evaporated. The residue was partitioned between ethyl acetate (100mL) and sodium hydrogen carbonate solution (100mL, 5% w/v). The layers were separated and the organic layer was dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (1:1, v/v) to give the title compound (0.29g) as a colourless gum.

(b) By proceeding in a similar manner to Reference Example 6(a) but using 5-{3-methyl-1-[(1-phenyl-ethylcarbamoyl)-methyl]-butyl}-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, diastereoisomer B [Reference Example 7(b)], and subjecting the crude product to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (1:2, v/v) there was prepared 3-(2,3-dihydro-1H-indol-5-yl)-5-methyl-hexanoic acid ethyl ester, enantiomer B as a colourless oil.

REFERENCE EXAMPLE 7

(a) 5-{2-Methyl-1-[(1-phenyl-ethylcarbamoyl)-methyl]-propyl}-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, diastereoisomer B

A solution of (R,S) 5-(1-carboxymethyl-2-methyl-propyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [3.7g, Reference Example 8(a)], (R)-(+)-α-methyl benzylaminc (1.5g), and diisopropylethylamine (7.8g) in dimethylformamide (50mL) was treated with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (4.6g). After standing

at room temperature overnight the mixture was partitioned between ethyl acetate (200mL) and hydrochloric acid (200mL, 1M) and the layers separated. The organic layer was washed with sodium hydrogen carbonate solution (200mL), then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane (3:7, v/v) to give, as the second eluate, the title compound (1.8g) as a white solid.

(b) By proceeding in a similar manner to Reference Example 7(a) but using (R,S) 5-(1-carboxymethyl-3-methyl-butyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [Reference Example 8(b)], and subjecting the crude product to flash chromatography on silica eluting with a mixture of ethyl acetate and pentane (2:5, v/v) there was obtained, as the first eluate, 5-{3-methyl-1-[(1-phenyl-ethylcarbamoyl)-methyl]-butyl}-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester, diastereoisomer B , as a colourless gum.

REFERENCE EXAMPLE 8

(a) (R,S) 5-(1-Carboxymethyl-2-methyl-propyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A solution of (R,S) 5-(1-ethoxycarbonylmethyl-2-methyl-propyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [3.9g, Reference Example 9(a)] in methanol (200mL) was treated with sodium hydroxide solution (30mL, 1M). After standing at room temperature overnight the mixture was evaporated to low bulk. The residue was diluted with water (100mL) then acidified with hydrochloric acid (50mL, 1M) and then extracted with ethyl acetate (100mL). The extract was washed with water, then dried and then evaporated to give the title compound (3.7g) as a colourless gum.

(b) By proceeding in a similar manner to Reference Example 8(a) but using (R,S) 5-(1-ethoxycarbonylmethyl-3-methyl-butyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [Reference Example 9(b)] there was prepared (R,S) 5-(1-carboxymethyl-3-methyl-butyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester as a colourless gum.

REFERENCE EXAMPLE 9

(a) (R,S) 5-(1-Ethoxycarbonylmethyl-2-methyl-propyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A solution of 5-(2-ethoxycarbonyl-1-isopropyl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [2.8g, Reference Example 10(a)] in ethanol (100mL) containing 10% palladium on charcoal (280mg) was hydrogenated at 65°C and atmospheric pressure overnight. After cooling to

room temperature the mixture was filtered through filter-aid. The filtrate was evaporated and the residue was dissolved in ethanol (100mL). This solution was treated with fresh catalyst (260mg) and the hydrogenation repeated at 75-80°C overnight. After cooling to room temperature the mixture was filtered through filter-aid and the filtrate evaporated to dryness. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and pentane (1:6, v/v) to give the title compound (2.6g) as a colourless oil.

(b) By proceeding in a similar manner to Reference Example 9(a) but using 5-(2-ethoxycarbonyl-1-isobutyl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester [Reference Example 10(b)] and carrying out the hydrogenation at 75-80°C for 36 hours and then at room temperature and 3 bar pressure of hydrogen for a further 5 hours there was prepared (R,S) 5-(1-ethoxycarbonylmethyl-3-methyl-butyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester as a colourless oil.

REFERENCE EXAMPLE 10

(a) 5-(2-Ethoxycarbonyl-1-isopropyl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A stirred suspension of 5-bromo-1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indole (3.0g, Reference Example 5), tetrabutylammonium bromide (650mg), and trans-di(μ-acetato) bis[σ-(di-*o*-tolylphosphino)benzyl]dipalladium (2) (180mg, prepared according to the method described in W. A. Herrmann et al., Angew. Chem. Int. Ed. Engl., 1995, vol. 34, page 1844) in dimethylformamide (30mL), under an atmosphere of argon, was treated with ethyl 3-methyl-but-2-enoate (2.1g, prepared according to the method described in M. W. Rathke, J. Org. Chem. 1985, vol. 50, page 2624) and diisopropylethylamine (2.9mL). This mixture was stirred at 135°C overnight then cooled to room temperature and then evaporated to low bulk. The residue was partitioned between ethyl acetate (80mL) and water (80mL). The layers were separated and the organic layer was washed with water, then with brine, then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and pentane (1:6, v/v) gave the title compound (2.8g) as a yellow oil.

(b) By proceeding in a similar manner to Reference Example 9(a) but using ethyl 5-methyl-hex-2-enoate (prepared according to the method described by K. Ando, Tetrahedron Letters, 1995, vol. 36, page 4105) to replace the ethyl 3-methyl-but-2-enoate and subjecting the crude product to flash chromatography on silica eluting with a mixture of ether and pentane mixture (1:6, v/v) there

was prepared 5-(2-ethoxycarbonyl-1-isobutyl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester as a yellow oil.

REFERENCE EXAMPLE 11

(a) (RS)-5-(2-Ethoxycarbonyl-1-furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A solution of (RS)-5-(2-ethoxycarbonyl-1-furan-3-yl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester (2.9g, Reference Example 12) in ethanol (100mL) was warmed to 60°C with stirring. This solution was treated with ammonium formate (10g), then with 10 % palladium on charcoal (900mg) in small portions under a blanket of nitrogen. After stirring at 60°C for 4 hours the mixture was allowed to cool to room temperature and filtered through filter-aid. The residue obtained on evaporation of the filtrate was partitioned between ethyl acetate (100mL) and water (100mL). The organic phase was dried and then evaporated to give the title compound (2.2g) as a colourless gum.

(b) By proceeding in a similar manner to Reference Example 11(a) but using of 5-(2-ethoxycarbonyl-1-thiophen-2-yl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester (3.7g, Reference Example 13) and subjecting the crude product to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane mixture (1:4, v/v) there was prepared (RS)-5-(2-ethoxycarbonyl-1-thiophen-2-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester as a yellow oil.

REFERENCE EXAMPLE 12

(RS)-5-(2-Ethoxycarbonyl-1-furan-3-yl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A mixture of ethyl 3-furan-3-yl-acrylate (2.9g, prepared according to the procedure described by Lunn et. al. in European Patent Application EP74268), 5-bromo-1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indole (4.0g, Reference Example 5), palladium acetate (200mg), *tris* (*o*-tolyl)phosphine (600mg) and tributylamine (7g) in dimethylformamide (40mL) was stirred at 130°C for 5 hours under an atmosphere of nitrogen. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (200mL) and hydrochloric acid (100mL, 0.2M). The organic phase was washed with aqueous sodium hydrogen carbonate solution (100mL, 5% w/v), then dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ether and pentane mixture (15:85, v/v) to give the title compound (2.9 g) as a colourless gum.

REFERENCE EXAMPLE 13

5-(2-Ethoxycarbonyl-1-thiophen-2-yl-vinyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

Triethyl phosphonoacetate (4.2g) was dissolved in anhydrous tetrahydrofuran (200mL) and treated in small portions with sodium hydride (750mg, 60 % suspension in oil). After stirring for about 15 minutes the clear solution was treated with 5-(thiophene-2-carbonyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester (3.4g, Reference Example 14) in one portion. The resulting mixture was stirred at reflux for 2 days then evaporated. The residue was partitioned between ethyl acetate (300mL) and brine (300mL). The organic phase was dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane mixture (1:4, v/v) to give the title compound (3.7 g) as a yellow oil.

REFERENCE EXAMPLE 14

5-(Thiophene-2-carbonyl)-2,3-dihydro-indole-1-carboxylic acid tertiary-butyl ester

A stirred solution of 5-bromo-1-tertiary-butyloxycarbonyl-2,3-dihydro-1H-indole (2g, Reference Example 5) in anhydrous tetrahydrofuran (50mL), at-70°C and under an atmosphere of nitrogen, was treated dropwise with a solution of butyllithium in hexanes (4.2mL, 1.6 M) whilst keeping the internal temperature at or below -60°C. The mixture was then treated with a solution of thiophene-2-carboxylic acid methoxy-methyl-amide (1.3g, Reference Example 15) in anhydrous tetrahydrofuran (10mL). The reaction mixture was allowed to warm to room temperature and then partitioned between ethyl acetate (100mL) and brine (200mL). The organic phase was dried and then evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and cyclohexane mixture (1:4, v/v) to give the title compound (1.7 g).

REFERENCE EXAMPLE 15

Thiophene-2-carboxylic acid methoxy-methyl-amide

Thiophene-2-carbonyl chloride (5g) was dissolved in dichloromethane (100mL) containing triethylamine (10g) and treated with solid *N,O*-dimethylhydroxylamine hydrochloride (4g). After stirring at room temperature overnight the mixture was diluted with fresh dichloromethane (100mL), then washed with hydrochloric acid (100mL), then with sodium hydrogen carbonate solution (100 mL, 5% w/v), then dried and then evaporated to give a yellow oil which slowly crystallised on standing to give the title compound.

IN VITRO AND IN VIVO TEST PROCEDURES

1. Inhibitory effects of compounds on VLA4 dependent cell adhesion to Fibronectin and VCAM.

1.1 Metabolic labelling of RAMOS cells.

RAMOS cells (a pre-B cell line from ECACC, Porton Down, UK) are cultured in RPMI culture medium (Gibco, UK) supplemented with 5% foetal calf serum (FCS, Gibco, UK). Prior to assay the cells are suspended at a concentration of 0.5 X 10^6 cells/ml RPMI and labelled with 400μCi/100mls of [^{3}H]-methionine (Amersham, UK) for 18 hours at 37°C.

1.2 96 well plate preparation for adhesion assay.

Cytostar plates (Amersham, UK) were coated with 50μl/well of either 3μg/ml human soluble VCAM-1 (R&D Systems Ltd, UK) or 28.8μg/ml human tissue Fibronectin (Sigma, UK). In control non-specific binding wells 50μl phosphate buffered saline was added. The plates were then left to dry in an incubator at 25°C, overnight. The next day the plates were blocked with 200μl/well of Pucks buffer (Gibco, UK) supplemented with 1% BSA (Sigma, UK). The plates were left at room temperature in the dark for 2 hours. The blocking buffer was then disposed of and the plates dried by inverting the plate and gently tapping it on a paper tissue. 50μl/well of 3.6% dimethyl sulfoxide in Pucks buffer supplemented with 5mM manganese chloride (to activate the integrin receptor Sigma, UK) and 0.2% BSA (Sigma, UK), was added to the appropriate control test binding and non-specific binding assay wells in the plate. 50μl/well of the test compounds at the appropriate concentrations diluted in 3.6% dimethyl sulfoxide in Pucks buffer supplemented with 5mM manganese chloride and 0.2% BSA, was added to the test wells.

Metabolically labelled cells were suspended at 4 x 10^6 cells/ml in Pucks buffer that was supplemented with manganese chloride and BSA as above. 50μl/well of cells in 3.6% dimethyl sulfoxide in Pucks buffer and supplements was added to all plate wells.

The same procedure exists for plates coated with either VCAM-1 or fibronectin and data is determined for compound inhibition of cell binding to both substrates.

1.3 Performance of assay and data analysis.

The plates containing cells in control or compound test wells are incubated in the dark at room temperature for 1 hour.

The plates are then counted on a Wallac Microbeta scintillation counter (Wallac, UK) and the captured data processed in Microsoft Excel (Microsoft, US). The data was expressed as an IC_{50},

namely the concentration of inhibitor at which 50% of control binding occurs. The percentage binding is determined from the equation:

$$\{[(C_{TB} - C_{NS})-(C_I - C_{NS})] / (C_{TB} - C_{NS})\}X\ 100 = \%\ \text{binding}$$

where C_{TB} are the counts bound to fibronectin (or VCAM-1) coated wells without inhibitor present, C_{NS} are the counts present in wells without substrate, and C_I are the counts present in wells containing a cell adhesion inhibitor.

The IC_{50}'s for inhibition of cell adhesion to fibronectin determined for the racemates of compounds of formula (I) compared to their corresponding active enantiomers are shown in Table 1.

TABLE 1

	IC_{50} for inhibition of cell adhesion to fibronectin
3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)- 3-phenyl-propionic acid, enantiomer A	0.4nM 2nM
racemate (IV)	3.2nM 3.6nM
3-(4-fluoro-phenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A	0.9nM 0.9nM
racemate (V)	5.2nM
3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid, enantiomer B	1.1nM
racemate (VI)	2.1nM 2.6nM
3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-5-methyl-hexanoic acid, enantiomer B	1.5nM
racemate (VII)	5.2nM
3-furan-3-yl-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A	4.0nM

racemate (II)	9.4nM
3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionic acid, enantiomer A	8.9nM
racemate (III)	13nM

2. Inhibition of antigen-induced airway inflammation in the mouse and rat.

2.1 Sensitization of the animals.

Rats (Brown Norway, Harland Olac, UK) are sensitized on days 0, 12 and 21 with ovalbumin (100 µg, intraperitoneally [i.p], Sigma, UK) administered with aluminium hydroxide adjuvant (100mg, i.p., Sigma, UK) in saline (1ml, i.p.).

In addition mice (C57) are sensitized on days 0 and 12 with ovalbumin (10µg, i.p.) administered with aluminium hydroxide adjuvant (20mg, i.p.) in saline (0.2ml, i.p.).

2.2 Antigen challenge.

Rats are challenged on any one day between days 28-38, while mice are challenged on any one day between days 20-30.

The animals are challenged by exposure for 30 minutes (rats) or 1 hour (mice) to an aerosol of ovalbumin (10g / l) generated by an ultrasonic nebulizer (deVilbiss Ultraneb, US) and passed into an exposure chamber.

2.3 Treatment protocols.

Animals are treated as required before or after antigen challenge. The aqueous-soluble compounds of this invention can be prepared in water (for oral, p.o. dosing) or saline (for intratracheal, i.t. dosing). Non-soluble compounds are prepared as suspensions by grinding and sonicating the solid in 0.5 % methyl cellulose / 0.2 % polysorbate 80 in water (for p.o. dosing, both Merck UK Ltd., UK) or saline (for i.t. dosing). Dose volumes are: for rats 1ml / kg, p.o. or 0.5mg / kg, i.t.; for mice 10ml / kg, p.o. or 1ml / kg, i.t.

2.4 Assessment of airway inflammation.

The cell accumulation in the lung is assessed 24 hours after challenge (rats) or 48-72 hours after challenge (mice). The animals are euthanized with sodium pentobarbitone (200mg/kg, i.p., Pasteur Merieux, France) and the trachea is immediately cannulated. Cells are recovered from the airway

lumen by bronchoalveolar lavage (BAL) and from the lung tissue by enzymatic (collagenase, Sigma, UK) disaggregation as follows.

BAL is performed by flushing the airways with 2 aliquots (each 10 ml/kg) RPMI 1640 medium (Gibco, UK) containing 10 % fetal calf serum (FCS, Serotec Ltd., UK). The recovered BAL aliquots are pooled and cell counts made as described below.

Immediately after BAL, the lung vasculature is flushed with RPMI 1640 / FCS to remove the blood pool of cells. The lung lobes are removed and cut into 0.5 mm pieces. Samples (rats: 400mg; mice: 150mg) of homogenous lung tissue are incubated in RPMI 1640 / FCS with collagenase (20 U/ml for 2 hours, then 60 U/ml for 1 hour, 37°C) to disaggregate cells from the tissue. Recovered cells are washed in RPMI 1640 / FCS.

Counts of total leukocytes recovered from the airway lumen and the lung tissue are made with an automated cell counter (Cobas Argos, US). Differential counts of eosinophils, neutrophils and mononuclear cells are made by light microscopy of cytocentrifuge preparations stained with Wright-Giemza stain (Sigma, UK). T cells are counted by flow cytometry (EPICS XL, Coulter Electronics, US) using fluophore-labelled antibodies against CD2 (a pan-T cell marker used to quantify total T cells), CD4, CD8 and CD25 (a marker of activated T cells). All antibodies were supplied by Serotec Ltd., UK)

2.5 Data analysis.

The cell data was expressed as mean cell numbers in unchallenged, challenged and vehicle treated, and challenged and compound treated groups, including the standard error of the means. Statistical analysis of the difference among treatment groups was evaluated using one-way analysis of variance via the Mann-Whitney test. Where $p < 0.05$ no statistical significance existed.

CLAIMS

What is claimed is:

1. A compound selected from:

3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionic acid, enantiomer A;

3-(4-fluoro-phenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, enantiomer A;

3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid, enantiomer B;

3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-5-methyl-hexanoic acid, enantiomer B;

3-furan-3-yl-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionic acid, and enantiomer A thereof;

3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionic acid, and enantiomer A thereof;

ethyl 3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-3-phenyl-propionate, enantiomer A;

ethyl 3-(4-fluorophenyl)-3-(1-{[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1H-indol-5-yl)-propionate, enantiomer A;

3-(2,3-dihydro-1*H*-indol-5-yl)-4-methyl-pentanoic acid ethyl ester, enantiomer B;

3-(2,3-dihydro-1H-indol-5-yl)-5-methyl-hexanoic acid ethyl ester, enantiomer B;

ethyl 3-furan-3-yl-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-propionate, enantiomer A;

(RS)-5-(2-Ethoxycarbonyl-1-furan-3-yl-ethyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester;

ethyl 3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionate, enantiomer A; and

ethyl (RS)-3-(1-{[3-methoxy-4-(3-*o*-tolyl-ureido)-phenyl]-acetyl}-2,3-dihydro-1*H*-indol-5-yl)-3-thiophen-2-yl-propionate;

and the corresponding N-oxides and prodrugs of such compounds; and pharmaceutically acceptable salts and solvates of such compounds and their corresponding N-oxides and prodrugs.

2. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 in association with a pharmaceutically acceptable carrier or excipient.

3. A compound according to claim 1 for use in therapy.

4. A compound according to claim 1 for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

5. A composition according to claim 2 for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

6. A compound according to claim 1 for use in the treatment of inflammatory diseases.

7. A composition according to claim 2 for use in the treatment of inflammatory diseases.

8. A compound according to claim 1 for use in the treatment of asthma.

9. A composition according to claim 2 for use in the treatment of asthma.

10. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

11. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of asthma.

12. A method for the treatment of a human or non-human animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion comprising administering to said patient an effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/00865

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/08 C07D405/06 C07D409/06 A61K31/405 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 23063 A (LAI JUSTINE YEUN QUAI ;MORLEY ANDREW DAVID (GB); RHONE POULENC ROR) 14 May 1999 (1999-05-14) claims 1,47,55-57 ---	1-12
P,X	WO 00 15612 A (COMMERCON ALAIN ;BOURZAT JEAN DOMINIQUE (FR); FILOCHE BRUNO JACQUE) 23 March 2000 (2000-03-23) cited in the application page 2, line 6 - line 13 page 25, line 14 -page 26, line 2 page 61, column 5, line 29 - line 32 page 148, line 18 - line 23 claims 1,91-95 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2001	25/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seymour, L

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim. A lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search does not include prodrugs of the claimed compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ional Application No
PCT/GB 01/00865

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WO 9923063 A	14-05-1999	AU 9755098 A	24-05-1999
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